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Gene Section
Short Communication

BUB1B (budding uninhibited by benzimidazoles 1 homolog beta (yeast))

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Identity

Other names: Bub1A, BUBR1, MAD3L, SSK1

HGNC (Hugo): BUB1B

Location: 15q15.1

DNA/RNA

Description

BUB1B spans 60 kb and is composed of 23 exons.

Protein

Protein name: BUBR1.

Description

1050 amino acids, 120 kDa.

Expression

Ubiquituously expressed.
Preferentially expressed in tissues with a high mitotic index.

Localisation

Cytoplasmic in interphase cells.
Bound to BUB3 or CENPE, it can be localised to nuclear kinetochores.
BUBR1 also localises to centrosomes during interphase.

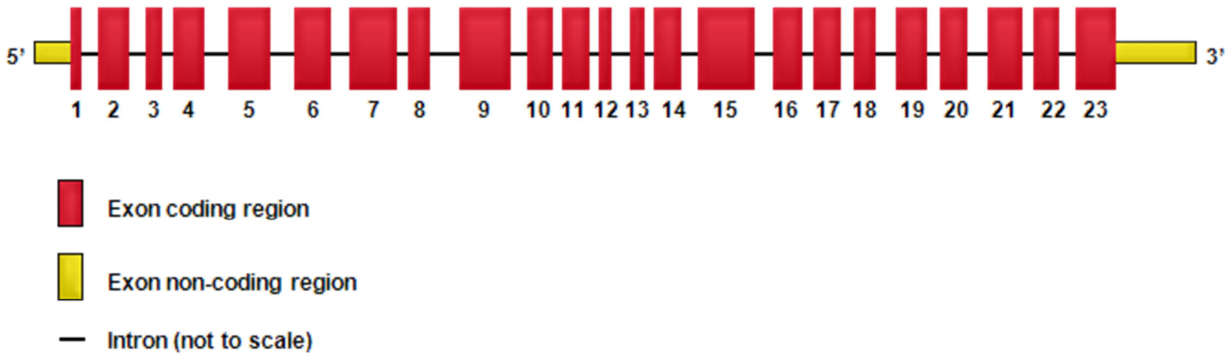

Figure 1. Schematic representation of BUB1B demonstrating the relative exon sizes.

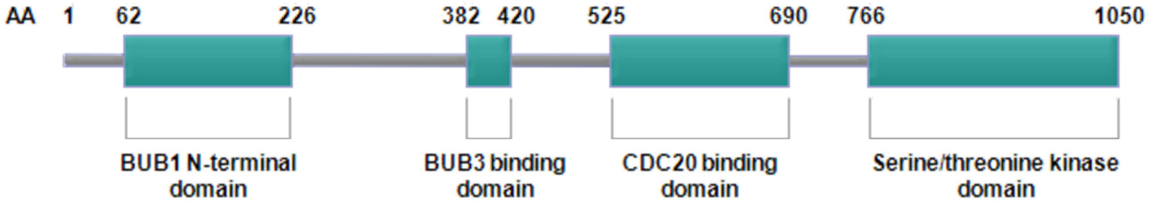

Figure 2. Schematic representation of BUBR1 demonstrating significant functional or structural domains.

Function

A central component of the mitotic spindle checkpoint that directly inhibits the anaphase-promoting complex/cyclosome until sister chromatids are correctly attached to the spindle, thus ensuring proper chromosome segregation during cell division. Also binds the motor protein CENPE, an interaction required for regulation of kinetochore-microtubule interactions and checkpoint signalling.

Homology

BUBR1 is the mammalian homologue of yeast Mad3, a significant difference being that BUBR1 possesses a kinase domain which is absent in Mad3.

Mutations

Note

Cells from BUB1B mutation-positive cases demonstrate an abnormal response to nocodazole-induced mitotic checkpoint activation.

Germinal

Biallelic germline mutations have been found in eight MVA pedigrees (figure 3).

Each family carries one missense mutation and one mutation that results in premature protein truncation or an absent transcript.

Monoallelic truncating mutations have also been reported in several cases.

Implicated in

Mosaic variegated aneuploidy (MVA)

Note

MVA is a rare recessive condition characterised by mosaic aneuploidies, predominantly trisomies and monosomies, involving multiple different chromosomes and tissues.

Affected individuals typically present with severe intrauterine growth retardation and microcephaly. Eye anomalies, mild dysmorphism, variable developmental delay and a broad spectrum of additional congenital abnormalities and medical conditions may also occur.

Prognosis

There is early mortality in a significant proportion of cases due to failure to thrive and/or complications of congenital abnormalities, epilepsy, infections or malignancy.

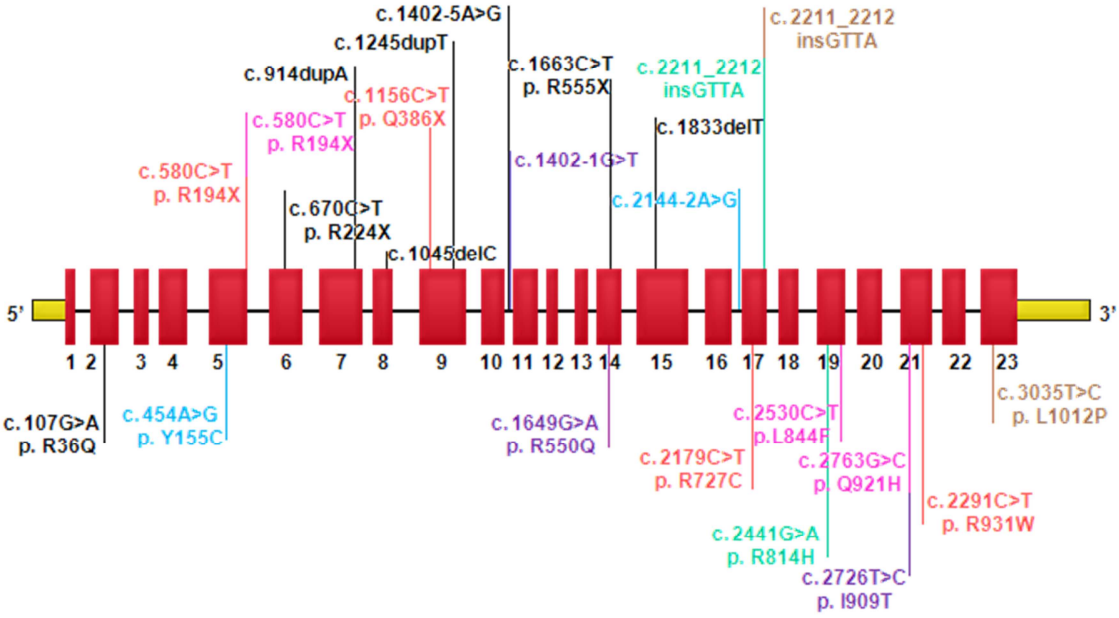

Figure 3. Schematic representation of BUB1B demonstrating the relative exon sizes and positions of known mutations. Truncating mutations are depicted above the figure, with missense mutations below. Biallelic mutations are represented by coloured lines, with mutations in the same individual in matching colours. Monoallelic mutations are represented by black lines and font.

Cytogenetics

The proportion of aneuploid cells varies but is usually >10% and is substantially greater than in normal individuals.

Oncogenesis

The risk of malignancy in MVA is high, with Wilms tumour, rhabdomyosarcoma, leukaemia and granulosa cell tumour of the ovary reported in several cases. Myelodysplastic syndrome has also been observed. Three of the eight cases with biallelic BUB1B mutations developed a rhabdomyosarcoma and one individual developed a granulosa cell tumour of the ovary. Wilms tumour and rhabdomyosarcoma have been reported in monoallelic BUB1B cases.

To be noted

Note

Biallelic mutations in CEP57 have also been identified in individuals with MVA syndrome.

References

Cahill DP, Lengauer C, Yu J, Riggins GJ, Willson JK, Markowitz SD, Kinzler KW, Vogelstein B. Mutations of mitotic checkpoint genes in human cancers. Nature. 1998 Mar 19;392(6673):300-3

Taylor SS, Ha E, McKeon F. The human homologue of Bub3 is required for kinetochore localization of Bub1 and a Mad3/Bub1-related protein kinase. J Cell Biol. 1998 Jul 13;142(1):1-11

Limwongse C, Schwartz S, Bocian M, Robin NH. Child with mosaic variegated aneuploidy and embryonal rhabdomyosarcoma. Am J Med Genet. 1999 Jan 1;82(1):20-4

Plaja A, Vendrell T, Smeets D, Sarret E, Gili T, Català V, Mediano C, Scheres JM. Variegated aneuploidy related to premature centromere division (PCD) is expressed in vivo and is a cancer-prone disease. Am J Med Genet. 2001 Jan 22;98(3):216-23

Lane AH, Aijaz N, Galvin-Parton P, Lanman J, Mangano R, Wilson TA. Mosaic variegated aneuploidy with growth hormone deficiency and congenital heart defects. Am J Med Genet. 2002 Jul 1;110(3):273-7

Bharadwaj R, Yu H. The spindle checkpoint, aneuploidy, and cancer. Oncogene. 2004 Mar 15;23(11):2016-27

Chen CP, Lee CC, Chen WL, Wang W, Tzen CY. Prenatal diagnosis of premature centromere division-related mosaic variegated aneuploidy. Prenat Diagn. 2004 Jan;24(1):19-25

Hanks S, Coleman K, Reid S, Plaja A, Firth H, Fitzpatrick D, Kidd A, Méhes K, Nash R, Robin N, Shannon N, Tolmie J, Swansbury J, Irrthum A, Douglas J, Rahman N. Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. Nat Genet. 2004 Nov;36(11):1159-61

Lampson MA, Kapoor TM. The human mitotic checkpoint protein BubR1 regulates chromosome-spindle attachments. Nat Cell Biol. 2005 Jan;7(1):93-8

Hanks S, Coleman K, Summersgill B, Messahel B, Williamson D, Pritchard-Jones K, Strefford J, Swansbury J, Plaja A, Shipley J, Rahman N. Comparative genomic hybridization and BUB1B mutation analyses in childhood cancers associated with mosaic variegated aneuploidy syndrome. Cancer Lett. 2006 Aug 8;239(2):234-8

Matsuura S, Matsumoto Y, Morishima K, Izumi H, Matsumoto H, Ito E, Tsutsui K, Kobayashi J, Tauchi H, Kajiwara Y, Hama S, Kurisu K, Tahara H, Oshimura M, Komatsu K, Ikeuchi T, Kajii T. Monoallelic BUB1B mutations and defective mitotic-spindle checkpoint in seven families with premature chromatid separation (PCS) syndrome. Am J Med Genet A. 2006 Feb 15;140(4):358-67

Musacchio A, Salmon ED. The spindle-assembly checkpoint in space and time. Nat Rev Mol Cell Biol. 2007 May;8(5):379-93

García-Castillo H, Vásquez-Velásquez AI, Rivera H, Barros-Núñez P. Clinical and genetic heterogeneity in patients with mosaic variegated aneuploidy: delineation of clinical subtypes. Am J Med Genet A. 2008 Jul 1;146A(13):1687-95

Izumi H, Matsumoto Y, Ikeuchi T, Saya H, Kajii T, Matsuura S. BubR1 localizes to centrosomes and suppresses centrosome amplification via regulating Plk1 activity in interphase cells. Oncogene. 2009 Aug 6;28(31):2806-20

Suijkerbuijk SJ, van Osch MH, Bos FL, Hanks S, Rahman N, Kops GJ. Molecular causes for BUBR1 dysfunction in the human cancer predisposition syndrome mosaic variegated aneuploidy. Cancer Res. 2010 Jun 15;70(12):4891-900

Snape K, Hanks S, Ruark E, Barros-Núñez P, Elliott A, Murray A, Lane AH, Shannon N, Callier P, Chitayat D, Clayton-Smith J, Fitzpatrick DR, Gisselsson D, Jacquemont S, Asakura-Hay K, Micale MA, Tolmie J, Turnpenny PD, Wright M, Douglas J, Rahman N. Mutations in CEP57 cause mosaic variegated aneuploidy syndrome. Nat Genet. 2011 Jun;43(6):527-9

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